PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

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ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 14 June 2007 (14.06.2007)	
Applicant's or agent's file reference NEREUS.109VP	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/043668	02 December 2005 (02.12.2005)	03 December 2004 (03.12.2004)

Applicant
DANA FARBER CANCER INSTITUTE et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference NEREUS.109VP	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/043668	International filing date *(day/month/year)* 02 December 2005 (02.12.2005)	Priority date *(day/month/year)* 03 December 2004 (03.12.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant DANA FARBER CANCER INSTITUTE		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 05 June 2007 (05.06.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Dorothée Mülhausen e-mail: pt01.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

REC'D 11 MAY 2006
WIPO PCT

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/043668	02.12.2005	03.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/397 A61P35/00

Applicant
NEREUS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Young, A Telephone No. +49 89 2399-7811

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-24 and 31-37

because:

☒ the said international application, or the said claims Nos. with respect to Industrial Applicability relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11, 31-37
	No:	Claims	12-30
Inventive step (IS)	Yes:	Claims	1-11, 37
	No:	Claims	12-36
Industrial applicability (IA)	Yes:	Claims	25-30
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III:

1. Claims 1-24 and 31-37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V:

2. The documents considered in the present processing are consecutively numbered D1-D6; this numbering results from the citations D1-D6 found in the International Search Report (ISR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

3. The application refers to a method of treating a neoplastic disease with a compound of formula (I), preferably salinosporamide A, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent. Further, a method of treating a neoplastic disease with a compound of formula (I) in combination with at least one additional chemotherapeutic agent and a pharmaceutical composition comprising a compound of formula (I) in combination with at least one additional chemotherapeutic agent is claimed. Finally, a method of treating a neoplastic disease comprising a synergistic combination of at least two proteosome inhibitors is claimed.

4. Novelty, Article 33(2) PCT

4.1 The subject-matter of claims 12-30 is considered to lack novelty over the disclosure of D1 within the meaning of Article 33(2) PCT for the following reasons:

D1 discloses salinosporamide A, which is encompassed by formula (I), for the treatment of neoplastic diseases, e.g. non-small-cell lung cancer or prostate cancer. Also the combination chemotherapy of salinosporamide compounds with other neoplastic agents, e.g. doxorubicin, tamoxifen is disclosed.

4.2. The subject-matter of claims 1-11 and 31-37 is novel over the cited prior art within the meaning of Article 33(2) PCT.

None of the cited references discloses a method of treating a neoplastic disease with a compound of formula (I), preferably salinosporamide A, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent.

Also a method of treating a neoplastic disease comprising a synergistic combination of at least two proteosome inhibitors is not found in the cited prior art.

5. Inventive step, Article 33(3) PCT

5.1 The object underlying the present application is the provision of a method of treating a neoplastic disease, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent.

The posed solution is the use of a compound of formula (I), preferably salinosporamide A.

The use of salinosporamide A for the treatment of neoplastic diseases is known from the cited prior art.
Document D2 discloses the in vitro cytotoxicity of salinosporamide A in different cancer cell lines.
However, the use for a salinosporamide for the treatment of a neoplastic disease, wherein the neoplastic disease is susceptible to resistance to at least one other chemotherapeutic agent is not known and also not suggested in the cited prior art.

Thus, an inventive step can be acknowledged for the subject-matter of claims 1-11 within the meaning of Article 33(3) PCT.

5.2 The subject-matter of claims 31-37 relates to a method of treating a neoplastic disease comprising a synergistic combination of at least two proteosome inhibitors.

Thus, the object underlying these claims is the provision of a method of treating a neoplastic disease.

The posed solution is a synergistic combination of at least two proteosome

inhibitors.

The application shows a synergistic effect for the combination of salinosporamide A and bortezomib.

However, a synergistic effect cannot be generalized to all possible combinations of at least two proteosome inhibitors.

In conclusion, an inventive step is acknowledged for the subject-matter of claim 37 within the meaning of Article 33(3) PCT.

The subject-matter of claims 31-36 does not involve an inventive step under Article 33(3) PCT.

6. Certain published documents (Rule 70.10)

D4: WO 2005/002572 A (NEREUS PHARMACEUTICALS, INC; PALLADINO, MICHAEL; NEUTEBOOM, SASKIA, TH) 13 January 2005 (2005-01-13)
D5: WILLIAMS PHILIP G ET AL: "New cytotoxic salinosporamides from the marine actinomycete Salinispora tropica" JOURNAL OF ORGANIC CHEMISTRY, vol. 70, no. 16, August 2005 (2005-08), pages 6196-6203, XP002376431 ISSN: 0022-3263
D6: MACHERLA VENKAT R ET AL: "Structure-activity relationship studies of salinosporamide a (NPI-0052), a novel marine derived proteasome inhibitor" JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 11, June 2005 (2005-06), pages 3684-3687, XP002376432 ISSN: 0022-2623

The above cited documents could become relevant by entering the regional European phase.